Modern Concepts of Cardiovascular Disease

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METABOLIC HEART DISEASES*

Definition

In the larger sense, all diseases of the heart are metabolic in origin: first, because the myocardium develops a defect in either the production of energy or its efficient conversion to mechanical work, the latter being the usual disturbance; second, because the metabolism of other organs and tissues must be adapted to reduced blood flow and hypoxia. In the narrower sense, the term "metabolic heart diseases" includes the cardiac manifestations of a number of well-defined or obscure general disorders of metabolism. In some of these, e.g., amyloidosis, glycogenosis, and lipochondrodystrophy (gargoylism), myocardial efficiency becomes impaired because of progressive mechanical encroachment of abnormal deposits within or between the muscle fibers. Related to this group is myocardial insufficiency in muscular dystrophies, in which the same pathology is found in heart muscle as in skeletal muscle. In others, as in beriberi, hyperthyroidism, myxedema, and hemochromatosis, the metabolic or enzyme machinery of the heart muscle itself is involved as part of a general cellular metabolic disturbance. In still another group, like Paget's disease of the bones, pregnancy or cirrhosis of the liver, the heart is ultimately overcome, in part, by the dynamic consequences of short circuiting of increased blood flow in the periphery, somewhat comparable to the effects of an arteriovenous fistula of large size. The remarkable influences of functioning metastatic carcinoid tumors on the cardiovascular system have been recently reviewed in this publication.[1] Finally, in the endomyocardial fibrosis so prevalent as a cause of heart failure in South African natives, prolonged protein malnutrition and the associated cytosiderosis and cirrhosis of the liver exert a mysterious effect on cardiac morphology and function. Whether the isolated cases of unexplained endocardial fibrosis reported from the United States, or fibroelastosis in adults dying of heart failure also represent end results of prolonged malnutrition is unknown.

The question may logically be raised whether arteriosclerotic heart disease is not equally a form of metabolic heart disease in view of current theories of atherosclerosis. However, the process is primarily related to the coronary arteries as part of the vascular tree. Similarly, hypertensive heart disease might be considered a later stage of a general vascular disturbance which, in turn, may have its origin in some general metabolic alteration. On the other hand, cardiac enlargement and heart failure resulting from abnormal hormonal production, as in pheochromocytomas, the Cushing syndrome or acromegaly, or aggravated by the administration of steroid hormones during the treatment of various diseases, do belong in the category of metabolic heart diseases. Fortunately, those conditions comprising the hormonal group are readily remediable if recognized in time. They will not be discussed further in this review.

It will be noted that metabolic heart disease comprises congenital, hereditary and acquired conditions of wide variety, that is, diseases of known and unknown etiologies, heart failure of both the low output or hypodynamic, the high output or hyperkinetic types, conditions completely remediable by specific treatment, and those with an inexorable progression in which only symptomatic therapy is possible.

Metabolic forms of heart disease are diagnosed largely after exclusion of the common etiological types and often with the aid of findings outside of the heart. Diagnosis in many instances is not made during life because of a low index of suspicion on the part of the physician.

Amyloidosis of the Heart

Excluding ordinary secondary amyloidosis of the heart, there remain two types of amyloid heart disease: The first and more important is part of *primary systemic amyloidosis*, well re-

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viewed by Lindsay, in 1946.[2] In addition to the heart, the amyloid deposits are found in the skin, gastrointestinal tract, lymph nodes, tongue, skeletal muscle, joints and tendons, hemopoietic system and small arteries. Cardiac involvement is found in 80 per cent at autopsy, is sufficient to produce congestive heart failure in 50 per cent of the patients, and death from this disturbance in 40 per cent. Heart failure results from a variety of amyloid lesions, such as diffuse or nodular myocardial deposits, infiltration of the visceral pericardium or endocardium, and involvement of the valves or of the coronary arteries. Combined lesions occur, giving rise to complex clinical pictures. In addition, signs and symptoms suggestive of heart failure may be caused by amyloid infiltration of the lungs (alveolar or vascular) of the trachea or mediastinal tissues. Chronic cor pulmonale may be produced. The diagnosis of the etiology of heart failure may, therefore, be quite difficult and, in the older age groups, is usually assumed to be arteriosclerotic heart disease. Constrictive pericarditis may be mimicked closely by amyloidosis of the heart muscle and the resulting restriction of myocardial contraction and relaxation. Even hemodynamic measurements and pressure tracings may be very similar in the two conditions.[3, 4] Electrocardiographic changes are nonspecific, including low voltage, T-wave changes and conduction disturbances.[5]

The problem of diagnosis, as in the case of other rare or atypical diseases, is largely a matter of awareness of the possibility of systemic amyloidosis. Once the thought, or hunch, has entered the physician's mind certain aids are available, such as the diffuse affection of bodily structures, and biopsy of a lymph node, skeletal muscle or other abnormal tissue. The Congo red test is seldom of value in primary amyloidosis. Recently, a new diagnostic test has been suggested. A familial series of 5 cases of primary systemic amyloidosis was discovered to have an atypical alpha-2 globulin in their serum electrophoretic pattern. On checking 66 members of 3 generations of the same family, Block, et al.,[6, 7] found no clinical signs or symptoms of amyloidosis in 37 individuals with a normal serum protein pattern, and 13 cases with some clinical signs among 29 with an atypical protein peak. Sixty per cent of the subjects with an abnormal protein pattern showed unexplained increases in some of the serum lipoprotein fractions. The authors concluded that primary systemic amyloidosis was, in part, an anomaly of lipoprotein metabolism inherited as a simple dominant pattern.

In contrast to primary systemic amyloidosis is the series of 29 cases of *primary cardiac amyloidosis* reviewed by Josselson, et al.,[8] in which the amyloid was virtually localized to the heart, chiefly in the form of gross atrial and endocardial deposits. In the myocardium, the amyloid was related to the reticulum fibers between the muscle cells and capillaries. Some amyloid was found in the vessel walls in the heart and, to a slight extent, in arteries of other organs. The striking feature was the advanced age of the affected subjects. Three were between 60 and 70 years of age at death, but the average age was 82 years. Males outnumbered females, 4 to 1. Carcinoma (gastrointestinal tract and prostate) was found in 12 subjects; multiple myeloma in 1. Congestive heart failure was observed in 6 cases, 4 of which were attributed to severe amyloidosis of the heart. In another autopsy series recently reported by Hüsselmann,[9] 40 out of 601 hearts showed histological evidence of amyloid. All but 3 were in individuals over 70 years old. The major causes of death were, in descending order, congestive heart failure, emphysema, malignant tumors, cerebral vascular accidents and a variety of infections. Though the clinical histories were poor, there was no obvious basis for amyloid. It was assumed that advanced age and changes in the proteins of body fluids and tissues were determining factors in the cardiovascular amyloid. Histochemical enzymatic reactions of the cardiac amyloid were, by and large, identical with those in secondary amyloidosis. The relation between this type of cardiac amyloidosis and the more dramatic systemic variety is undetermined.

Glycogenosis of the Heart

This is a rare disease of infants who usually die within the first year after displaying difficulty in feeding, cyanosis, dyspnea, cardiomegaly and signs of congestive heart failure. They also manifest muscular weakness, neurologic changes, and a large tongue. Di Sant'Agnese, et al.,[10, 11] reported 2 cases in siblings, and their findings were confirmed by Childs, et al.[12] Significantly, these patients have a completely normal carbohydrate metabolism, including a normal breakdown of cardiac and hepatic glycogen post mortem. While glycogen is found in many organs and tissues, this disease seems basically different from the classical von Gierke's disease and from the hepatic type of glycogen storage disease.[13] In fact, the hepatic and cardiac types have never been reported in the same family.[10, 11] Diagnosis during life may be difficult since the cardiac and ECG findings are nonspecific, and the patient's general appearance may simulate hypothyroid, mongoloid or amyotonic states. A skeletal muscle biopsy may help by revealing glycogen. Treatment is symptomatic.

Gargoylism (Lipochondrodystrophy)

This is a rare type of storage disease in which a complex, macromolecular, glycoprotein material accumulates in many cells of the body. The afflicted subjects may survive through childhood and early adult decades. Familial involvement

has been described.[14] Reilly and Lindsay[15, 16, 17] reviewed the clinical and pathological findings, emphasizing the bony distortion which produces the hideous facies, dwarfism, kyphosis, and other manifestations, such as large tongue, hepatosplenomegaly, cloudy corneas, deafness, mental deficiency, peg teeth, clawed hands, hirsutism and cardiomegaly. About 70 per cent of the patients have cardiovascular disease and commonly die from congestive heart failure at an average age of 11 years. In the heart, the mitral valve is always affected by nodular thickening with gelatinous material; other valves, the aorta, and the intima of pulmonary and coronary arteries may also be involved. Glomerulonephritic lesions are common. It is chiefly the fibroblastic cells that are swollen and vacuolated by the abnormal glycoprotein deposit. Carbohydrate metabolism is grossly normal by clinical tests. There is no known etiology or specific treatment for gargoylism.

Hemochromatosis of the Heart

Heart failure probably has become a more frequent cause of death in hemochromatosis since the prolongation of life in bronze diabetes by insulin, and the increasing use of multiple blood transfusions in anemias. It has been estimated that heart failure is the major cause of death in 15 to 20 per cent of the cases of hemochromatosis.[18] Lewis, in 1954,[19] described two cases of generalized hemosiderosis, and reviewed the entire subject in the light of the various etiologies of hemosiderosis—inborn error of metabolism, multiple blood transfusions, and the nutritional disorders leading to cytosiderosis. Cardiac hemosiderosis is associated with general enlargement of the heart and iron pigment deposition in the fibers, which show degeneration but no fibrosis. Arrhythmias, including auricular fibrillation and conduction disturbances, are common. The ECG shows low voltage and flat T-waves.

Diagnosis is difficult in the absence of glycosuria and pigmentation of the skin (case 1 of Lewis), particularly since hepatomegaly or cirrhosis are so common apart from hemochromatosis. When the diagnosis is thought of in unexplained severe heart failure, it may be established by examination of sternal marrow for clumps of hemosiderin, measurement of serum iron and iron-binding capacity, and liver biopsy. Recognition of cardiac hemosiderosis during life is important because de-ironization is feasible and may prevent ultimate heart failure.

Recently, emphasis has been laid upon the familial occurrence of hemochromatosis, including involvement of the heart.[18] In one family, three brothers in their forties were discovered to have the disease in an advanced form. One died of severe, rapidly developing heart failure associated with auricular flutter, wide QRS and low T-waves. At autopsy, no other basis than hemosiderosis of the myocardium was found to explain the heart failure. The children of the patients were clinically healthy, but had elevated serum iron levels.

Muscular Dystrophies of the Heart

Autopsy reveals that progressive muscular dystrophies are associated with myocardial involvement in about half of the cases. One third of the deaths have been attributed to heart failure. During life, a variety of ECG changes, largely tachycardia, short P-R intervals, abnormal P-waves and deep Q-waves, with widened QRS, have been described.[20, 21] Symptoms of cardiac failure are usually absent, probably because of prolonged bed rest and inactivity. However, sudden heart failure may occur terminally or be remediable if recognized and treated in time. At autopsy, in a series of 11 patients[22] myocardial lesions were found in 6, consisting of interstitial fibrosis up to massive scars, with or without fatty cell replacement, swelling, vacuolation and fragmentation of entrapped fibers, little or no involvement of the endocardium, valves or epicardium, and slight inflammatory reaction in the stroma of the unscarred myocardium. There was no relation between duration and severity of disease of the skeletal musculature and the degree of myocardial involvement. In view of the essential identity of the pathological process in the heart muscle and skeletal muscle, patients with progressive muscular dystrophy should be considered as candidates for cardiac failure and treated accordingly.

Beriberi Heart Disease

Beriberi heart disease is a well recognized type of metabolic disturbance in which the heart itself also suffers from a lack of cocarboxylase. Typically, it is associated with a high output and stroke volume during congestive failure, and is unresponsive to exercise except for a marked increase in pulmonary artery pressures.[23, 24, 25] Peripheral vasodilatation, bounding pulse, increased pulse pressure, normal or short circulation time, and reduced A-V oxygen difference occur in a variable percentage of cases. In the last 20 years, the criteria for the diagnosis of beriberi heart disease in the Occident have been considerably modified from the classical description of the disease in the Orient. This has been necessitated by the wide geographical differences in nutritional factors, including *alcoholism*, and the realization that many remediable "atypical" cases were being overlooked and allowed to progress into the chronic intractable heart failure of irreversible myocardial fibrosis.[26] In 1946, Blankenhorn, et al.,[27] set up the following diagnostic criteria for Occidental beriberi heart disease: (1) unclear etiology; (2) history of three or more months on

a thiamine-deficient diet (alcoholism was always involved); (3) signs of peripheral neuritis or pellagra; (4) enlarged heart, with regular sinus rhythm; (5) edema, high venous pressure, anemia and hypoproteinemia; (6) minor ECG changes; and (7) recovery with decrease in heart size on specific treatment or confirmation of the diagnosis by autopsy findings. In this series of 12 cases, there was only one female and less than 50 per cent showed the classical Wenckebach signs of beriberi heart failure. The response to large intravenous doses of thiamine was not dramatic and rather slow.

Benchimol and Schlesinger, in 1953,[28] confirmed the preceding criteria in 22 cases in Brazil. All were males and alcoholic. Both left and right heart failure were present in the absence of a hyperkinetic syndrome, in 50-75 per cent of the patients. Edema was an early sign, along with dyspnea and pulmonary congestion. Cyanosis and palpitation were rare. Gallop rhythm, tachycardia and accentuated second pulmonic tone were constant. Transient arterial hypertension occurred during failure. High venous pressure and polyneuritis were observed in all cases, and regular sinus rhythm in all but one subject. The heart size returned to normal in only 40 per cent after specific treatment. The nonspecific ECG changes of low voltage and negative T-waves were reversible. The authors pointed out the lack of response to thiamine alone in the later stages of the disease, and the favorable influence of the usual management of heart failure in some patients.

The role of vigorous *exercise* in modifying the clinical picture of acute beriberi heart failure was strikingly shown in the report by Walters[29] of a series of 11 cases of severe cardiac edema in previously healthy young pearl divers in Kuwait. They had been on a poor diet, chiefly spoiled rice, for weeks or months while out on a pearl fishing trip. They showed little or no peripheral neuritis but *acute arterial hypertension* (in 7 cases) to the point of death from left ventricular failure in one case and severe cerebral symptoms in others. Presumably, vasoconstriction occurred at a time of increased circulating blood volume. In addition to thiamine, a methonium compound was given successfully in one patient with acute hypertension. Recovery was prolonged in most cases and failed to occur in some.

The physiological changes in beriberi heart failure are unique because they are associated with reduced *myocardial energy production.* As a result of thiamine deficiency, the proper completion of carbohydrate metabolism in the citric acid cycle is prevented by a block between pyruvate and acetyl coenzyme A. The myocardial utilization of pyruvate and lactate is impaired,[30–33] and the extraction of both these metabolites is inhibited. Fatty acid catabolism, an important source of myocardial energy, is also adversely affected through the lack of cocarboxylase as a flavin cofactor. Myocardial oxygen extraction and consumption are much reduced as part of the metabolic block. These myocardial metabolic changes in beriberi heart failure differ strikingly from those in the commoner etiological types in which myocardial metabolism and energy production are essentially unimpaired, but there is inefficient utilization of the energy for contraction by the physicochemically altered myofibrils.[32] In prolonged beriberi heart disease, perhaps, failure may be irreversible because the chronically overstretched myocardial fibers may no longer utilize energy efficiently, in spite of restoration of energy production by specific treatment. The lack of satisfactory response of beriberi heart failure to digitalis is understandable because this drug does not act on the mitochondria, the site of energy production in the myocardial fibril.[30, 31]

Thyroid Heart Disease

Heart disease related to hyperthyroidism or myxedema, natural or induced, has been recently reviewed.[34, 35] As has been frequently pointed out, *hyperthyroidism* in the younger age groups rarely leads to heart failure unless rheumatic or other organic heart disease coexists. However, there is the possibility of relative thiamine deficiency complicating the hypermetabolic high cardiac output and leading to heart failure.[26] In the older age groups, hypertensive and arteriosclerotic heart disease can be aggravated by prolonged masked hyperthyroidism which may underlie the unusual weakness, arrhythmias unresponsive to digitalization, or unexplained tachycardias.[34] The radioiodine uptake by the thyroid is a valuable diagnostic test, but may be misleading in either direction as a result of the unsuspected influence of salt-poor diets (iodine deficiency), thyroactive drugs (iodides, sulfonamides, adrenal steroids, radiographic media, etc.) or even previous surgical or radioiodine thyroidectomy. In case of doubt or discrepancy from the clinical judgment, determination of the protein-bound iodine in the serum, the hormonal radioiodine conversion ratio and the response of the radioiodine uptake to thyroid hormone will help settle the diagnosis and point to the appropriate treatment. The use of radioiodine has greatly simplified the management of hyperthyroidism as a cause of heart failure.

Recent studies by Rowe, et al.,[36] by means of cardiac catheterization in thyrotoxic patients have demonstrated a significant increase in the coronary blood flow, the heart's own oxygen consumption and the metabolic rate per beat during the hyperthyroid state. After adequate treatment of hyperthyroidism, myocardial metabolism and coronary blood flow returned to normal. This hypermetabolism of the myocardium must be considered a burden, in addition to the in-

creased cardiac output and work imposed by the hypermetabolism of the body as a whole. Leight, et al.,[37] also found increased coronary flow per unit of left ventricular weight in hyperthyroidism, but not disproportionate to the increased cardiac output. The coronary vascular resistance was reduced and myocardial oxygen consumption increased, but again in proportion to the total body oxygen consumption. Carbohydrate metabolism of the heart was normal. These authors concluded that thyroid hormone had no unique effect on the heart. The problem still remains unsettled.

As to *myxedema*, the presence of a low cardiac output is compatible with the absence of heart failure, as long as it parallels the reduced oxygen consumption of the body. Cardiac catheterization in a few such patients has demonstrated normal cardiopulmonary pressures, even though their hearts were enlarged and their ECG's abnormal, suggesting cardiac damage or pericardial effusion.[35] In two patients with some symptoms and signs of heart failure, the cardiac output was reduced out of proportion to the low oxygen consumption; right ventricular and pulmonary arterial pressures rose on exercise. Interpretation of data in these cases is difficult because most of the patients are in the older, possibly coronary atherosclerotic, age group. The question as to the advantages of therapeutic hypothyroidism for heart failure or coronary insufficiency has not been satisfactorily answered.

Heart Failure in Pregnancy, Paget's Osteitis, and Cirrhosis of the Liver

Heart failure of the high output type occurs in these conditions and, to a significant extent, is the result of the abnormal hemodynamics of arteriovenous communications or other short-circuiting shunts of some magnitude. It may be questioned, then, whether metabolic heart disease is involved. Indirectly, however, the peculiar system of blood flow, at least in pregnancy and Paget's disease, represents increased metabolism in the uterine contents and the affected bones, respectively. In the case of *pregnancy*, the previously normal heart can tolerate the extra burden, but the rheumatic heart with a tight mitral valve is liable to decompensation and must be carefully protected against unnecessary demands. This subject has been excellently reviewed by Burwell and Metcalfe.[38, 39]

The striking increase in blood flow and decrease in A-V oxygen difference in the affected limbs of patients with active *Paget's disease of the bones* have been associated with variable increases in cardiac output—in 5 cases, 7-13 liters per minute.[40] Heart failure occurred in some of the patients who had enlarged left ventricles. There was a rough correlation between the elevation of cardiac output and the estimated percentage of skeletal involvement. No case in this group of Howarth's, however, was studied cardiodynamically during heart failure. Therefore, other investigators[41] have questioned the validity of the findings and the conclusions that the cardiac failure was the result of direct A-V communications. While confirming the increased peripheral blood flow and arterialization in the affected bones, they observed a normal cardiac output *at rest* in cases of generalized Paget's disease; also normal cardiopulmonary pressures, cardiac work and peripheral resistances. During *exercise* there was a mildly disproportionate rise in cardiac index for the oxygen consumed, just as in systemic A-V aneurysms. The question of cardiac failure arising on this basis alone remains an open one for the present, especially since Paget's disease affects chiefly the older age groups, and because of the marked variations in activity of the disease, giving the heart some respite from overwork. Unfortunately, no specific therapeutic test is available.

In *cirrhosis of the liver*, a number of factors may contribute to the development of heart failure: the undetermined effect of malnutrition and disturbed metabolism on myocardial function; the cardiodynamic effects of the abnormal venous shunting between the portal and systemic systems; the increased blood volume associated with extensive collateral circulation; and the abnormal retention of sodium related to a number of factors, including possible impairment of inactivation of electrolyte regulating hormones. Nevertheless, gross cardiac enlargement and obvious congestive heart failure are uncommon in the absence of underlying organic heart disease.

Heart Disease in Chronic Malnutrition—Endomyocardial Fibrosis

This is a large group of what may be related conditions beginning with *cardiac atrophy* and resultant circulatory changes in various types of emaciation, either due to primary inanition or commonly associated with chronic infection, malignant neoplasms or diseases of the gastrointestinal tract, with obstruction or malabsorption. Heart failure is rarely manifested during the period of body wasting.[42] Such hearts, however, may tolerate poorly sudden attempts at renutrition and react with signs and symptoms of acute congestive failure.[43]

A specific type of *nutritional heart disease* has been described in recent years by Gillanders, et al.,[44, 45] in which a very low cardiac output was found, in contrast to beriberi heart disease. This malnutritional heart failure was commonly observed in adult urbanized Bantus of South Africa, who lived on a high carbohydrate (refined maize and sugar) and very low protein diet, with little fruit or vegetables. The subjects developed massive edema and ascites, hydrothorax, and even hydroarthrosis and hydroceles. The ascitic fluid had a high protein content. The heart was

markedly enlarged, showed poor pulsation, but little pericardial fluid. Diastolic gallop rhythm, high venous pressure, prolonged circulation time, small pulse, large hard liver, pulmonary congestion, and ECG changes of subepicardial injury were characteristic signs. These patients, though far advanced in their disease, responded to bed rest and a nutritious diet, irrespective of salt restriction, thiamine supplements, digitalis, mercurials, testosterone or alpha-tocopherol. Relapse could be induced in a few weeks by return to the original inadequate diet and physical activity. While the heart size might return to normal or be markedly reduced, the liver remained large. Biopsy of the liver showed, in 19 out of 22 cases, marked cytosiderosis and varying degrees of fibrosis. In view of the autopsy findings of generalized hemosiderosis,[45] it was assumed that the adult syndrome involving the heart probably dated from childhood kwashiorkor disease. Presumably, it required many years to bring about gross cardiac insufficiency, but once this happened the heart seemed to be sensitized to a poor diet. The role of the chronic liver failure in this process was mysterious.

It is interesting that the hypertrophied myocardium itself showed no hemosiderosis or excessive glycogen, no significant fibrosis or necrosis, and no hydropic degeneration. There was evidence, however, of moderate interfibrillary edema. The valves, coronary arteries and aorta were essentially normal. Pulmonary embolism from organizing ventricular mural thrombosis was commonly found; systemic embolism was also observed, but less frequently.

A somewhat different variety of possibly malnutritional heart disease, responsible for nearly 15 per cent of all deaths from congestive heart failure in natives of Uganda (East Africa), has been reported by Ball, Williams and Davies.[46, 47] In this group the clinical course varied from a few months to two years, and the heart failure in most cases was due to organic mitral, less often tricuspid, insufficiency. In a few cases, constrictive pericarditis was closely simulated clinically. Response to treatment was poor once heart failure had developed.

The pathological findings in the heart consisted of a striking *endocardial fibrosis* in both ventricles, with variable subendocardial myocardial necrosis and organizing mural thrombosis. Curiously, embolism was rare in this series. The fibrosis began in the apex of each ventricle and extended along the posterior wall, engulfing the papillary muscle, some chordae tendineae and the posterior mitral or tricuspid valve leaflet, which became adherent to the wall and produced valvular insufficiency. In extreme cases, the right ventricular cavity was almost completely obliterated, giving rise mechanically to the same dynamic effects as constrictive pericarditis. Subacute bacterial endocarditis was superimposed on 20 per cent of the damaged mitral valves. The etiology of the postulated initial myocardial lesion, whether viral, allergic or nutritional, was not determinable. It was suggested that endocardial damage was followed by early thrombosis, organization of thrombi and fibrosis, late secondary thrombosis with occlusion of thebesian and arterioluminal vessels, and further myocardial damage.

Another series of 40 autopsied cases was reported from South Africa by Becker, et al.,[48] in which the findings of the two previous varieties of endomyocardial fibrosis were, to some extent, combined. No valvular fibrosis was described in this group, but there was a larger proportion of acute and subacute endocardial lesions with "mucinous edema," fibrinoid necrosis, and organizing polypoid verrucae in the venous sinuses of the subendocardial myocardium. The authors considered these changes as a form of cardiac "collagenosis," and related the process to Selye's "cardiovascular hyalinosis." This viewpoint has been vigorously disputed by others.

The important fact remains that a remarkably large percentage of deaths from congestive heart failure in African natives, generally in a chronically malnourished state, are associated with *endomyocardial necrosis and fibrosis* of varying degrees and unknown duration. In the United States, somewhat similar though very isolated cases have been reported as instances of cardiac hypertrophy and failure of unknown origin, without specific emphasis on malnutrition in their etiology.[49, 50] An important exception is the paper by Smith and Furth, in 1943,[51] on three patients with congestive heart failure and dietary deficiency, unresponsive to vitamin B. The autopsies revealed myocardial and endocardial fibrosis of the ventricles without obvious basis. The authors postulated a nutritional factor in the initial myocardial degeneration and later implication of the subendocardial blood supply by endocardial fibrosis.

The relationship of the adult type of *endocardial fibroelastosis* decribed by Thomas, et al.,[52] to the preceding varieties of endomyocardial fibrosis is an interesting and disputed problem, which only the careful study of a much larger series of cases may clarify. Certainly the infantile and childhood groups of fibroelastosis do not result from a general nutritional disturbance, but probably are an expression of some congenital anomaly in development, with anoxia as the final common factor in the failure of the left ventricle, so characteristic of these cases.[53, 54, 55]

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REFERENCES

1. Mattingly, T. W., and Sjoerdsma, A.: The cardiovascular manifestations of functioning carcinoid tumors. Mod. Concepts Cardiovas. Dis. **25**: 337, 1956.
2. Lindsay, S.: The heart in primary systemic amyloidosis. Am. Heart J. **32**: 419, 1946.
3. Findley, J. W., Jr., and Adams, W.: Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia. Arch. Int. Med. **81**: 342, 1948.
4. Gunnar, R. M., Dillon, R. F., Wallyn, R. J., and Elisberg, E. I.: Physiologic and clinical similarity between primary amyloid of the heart and constrictive pericarditis. Circulation **12**: 827, 1955.
5. Josselson, A. J., and Pruitt, R. D.: Electrocardiographic findings in cardiac amyloidosis. Circulation **7**: 200, 1953.
6. Block, W. D., Rukavina, J. G., and Curtis, A. C.: Serum electrophoretic studies on patients with familial primary systemic amyloidosis. J. Lab. and Clin. Med. **47**: 357, 1956.
7. Rukavina, J. G., Block, W. D., and Curtis, A. C.: Familial primary systemic amyloidosis: an experimental, genetic and clinical study. J. Invest. Dermat. **27**: 111, 1956.
8. Josselson, A. J., Pruitt, R. D., and Edwards, J. E.: Amyloid localized to heart; analysis of 29 cases. A.M.A. Arch. Path. **54**: 359, 1952.
9. Husselmann, H.: Beitrag zum Amyloid-problem auf Grund von Untersuchungen an menschlichen Herzen. Virchows Arch. path. Anat. **327**: 607, 1955.
10. di Sant'Agnese, P. A., Andersen, D. H., Mason, H. H., and Bauman, W. A.: Glycogen storage disease of heart; report of 2 cases in siblings with chemical and pathologic studies. Pediatrics **6**: 402, 1950.
11. di Sant'Agnese, P. A., Andersen, D. H., and Mason, H. H.: Glycogen storage disease of heart; critical review of literature. Pediatrics **6**: 607, 1950.
12. Childs, A. W., Crose, R. F., and Henderson, P. H.: Glycogen disease of heart; report of 2 cases occurring in siblings. Pediatrics **10**: 208, 1952.
13. Recant, L.: Recent developments in the field of glycogen metabolism and the diseases of glycogen storage. Am. J. Med. **19**: 610, 1955.
14. Emanuel, R. W.: Gargoylism with cardiovascular involvement in two brothers. Brit. Heart J. **16**: 417, 1954.
15. Reilly, W. A., and Lindsay, S.: Gargoylism (lipochondrodystrophy); review of clinical observations in 18 cases. Am. J. Dis. Child. **75**: 595, 1948.
16. Lindsay, S., Reilly, W. A., Gotham, T. J., and Skahen, R.: Gargoylism; study of pathologic lesions and clinical review of 12 cases. Am. J. Dis. Child. **76**: 239, 1948.
17. Lindsay, S.: Cardiovascular system in gargoylism. Brit. Heart J. **12**: 17, 1950.
18. Kappeler, R.: Familiäre Hämochromatose; zugleich ein Beitrag zur Frage der Herzinsuffizienz und zur Aderlasstherapie bei Hamochromatose. Schweiz. med. Wschr. **86**: 477, 1956.
19. Lewis, H. P.: Cardiac involvement in hemochromatosis. Am. J. Med. Sci. **227**: 544, 1954.
20. Rubin, I. L., and Buchberg, A. S.: The heart in progressive muscular dystrophy. Am. Heart J. **43**: 161, 1952.
21. Weisenfeld, S., and Messinger, W. J.: Cardiac involvement in progressive muscular dystrophy. Am. Heart J. **43**: 170, 1952.
22. Nothacker, W. G., and Netsky, M. G.: Myocardial lesions in progressive muscular dystrophy. Arch. Path. **50**: 578, 1950.
23. Burwell, C. S., and Dexter, L.: Beriberi heart disease. Tr. Assn. Am. Physn. **60**: 59, 1947.
24. Campbell, J. A., Selverstone, L. A., and Donovan, D. L.: Studies on high output cardiac failure of occidental beriberi (Abstract). J. Clin. Invest. **30**: 632, 1951.
25. Iseri, L. T., Uhl, H. S. M., Chandler, D. E., Boyle, A. J., and Myers, Gordon B.: Fluid and electrolyte balance during recovery from high-output heart failure due to beriberi. Circulation **9**: 247, 1954.
26. Weiss, S., and Wilkins, R. W.: Nature of cardiovascular disturbances in vitamin deficiency states. Tr. Assn. Am. Physn. **51**: 341, 1936.
27. Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Austin, R. S.: Occidental beriberi heart disease. J.A.M.A. **131**: 717, 1946.
28. Benchimol, A. B., and Schlesinger, P.: Beriberi heart disease. Am. Heart J. **46**: 245, 1953.
29. Walters, J. H.: Hyperpiesis in cardiovascular beriberi. Quart. J. Med. **22**: 195, 1953.
30. Bing, R. J.: Metabolism of the heart. Harvey Lectures, Series L., 1954-55, p. 27.
31. Bing, R. J.: Myocardial metabolism. Circulation **12**: 635, 1955.
32. Olson, R. E., and Schwartz, W. B.: Myocardial metabolism in congestive heart failure. Medicine **30**: 21, 1951.
33. Hackel, D. B., Goodale, W. T., and Kleinerman, J.: Effect of thiamin deficiency on myocardial metabolism in intact dogs. Am. Heart J. **46**: 883, 1953.
34. Stanbury, J. B.: Thyroid gland in relation to heart disease. Mod. Concepts Cardiovas. Dis. **21**: 134, 1952.
35. Ellis, L. B., Mebane, J. G., Maresh, G., Hultgren, H. N., and Bloomfield, R. A.: Effect of myxedema on the cardiovascular system. Am. Heart J. **43**: 341, 1952.
36. Rowe, G. G., Huston, J. H., Weinstein, A. B., Tuchman, H., Brown, J. F., and Crumpton, C. W.: The hemodynamics of thyrotoxicosis in man with special reference to coronary blood flow and myocardial oxygen metabolism. J. Clin. Invest. **35**: 272, 1956.
37. Leight, L., DeFazio, V., Talmers, F. N., Regan, T. J., and Hellems, H. K.: Coronary blood flow, myocardial oxygen consumption, and myocardial metabolism in normal and hyperthyroid human subjects. Circulation **14**: 90, 1956.
38. Burwell, C. S., and Metcalfe, J.: Heart disease and pregnancy. Mod. Concepts Cardiovas. Dis. **23**: 250, 1954.
39. Burwell, C. S.: Circulatory adjustments to pregnancy (Thayer lecture). Bull. Johns Hopkins Hosp. **95**: 115, 1954.
40. Howarth, S.: Cardiac output in osteitis deformans. Clin. Sci. **12**: 271, 1953.
41. Lequime, J., and Denolin, H.: Circulatory dynamics in osteitis deformans. Circulation **12**: 215, 1955.
42. Hellerstein, H. K., and Santiago-Stevenson, D.: Atrophy of the heart: a correlative study of eighty-five proved cases. Circulation **1**: 93, 1950.
43. Keys, A.: Cardiovascular effects of undernutrition and starvation. Mod. Concepts Cardiovas. Dis. **17**: 21, 1948.
44. Gillanders, A. D.: Nutritional heart disease. Brit. Heart J. **13**: 177, 1951.
45. Higginson, J., Gillanders, A. D., and Murray, J. F.: Heart in chronic malnutrition. Brit. Heart J. **14**: 213, 1952.
46. Ball, J. D., Williams, A. W., and Davies, J. N. P.: Endomyocardial fibrosis. Lancet **1**: 1049, 1954.
47. Davies, J. N., and Ball, J. D.: The pathology of endomyocardial fibrosis in Uganda. Brit. Heart J. **17**: 337, 1955.
48. Becker, B. J. P., Chatgidakis, C. B., and Van-Lingen, B.: Cardiovascular collagenosis with parietal endocardial thrombosis: a clinicopathologic study of forty cases. Circulation **7**: 345, 1953.
49. Elster, S. K., Horn, H., and Tuchman, L. R.: Cardiac hypertrophy and insufficiency of unknown etiology. Am. J. Med. **18**: 900, 1955.
50. McKusick, V. A., and Cochran, T. H.: Constrictive endocarditis. Bull. Johns Hopkins Hosp. **90**: 90, 1952.
51. Smith, J. J., and Furth, J.: Fibrosis of endocardium and myocardium with mural thrombosis; notes on its relation to isolated (Fiedler's) myocarditis and to beriberi heart. Arch. Int. Med. **71**: 602, 1943.
52. Thomas, W. A., Randall, R. V., Bland, E. F., and Castleman, B.: Endocardial fibroelastosis, a factor in heart disease of obscure etiology: a study of 20 autopsied cases in children and adults. New England J. Med. **251**: 327, 1954.
53. Adams, F. H., and Katz, B.: Endocardial fibroelastosis; case reports with special emphasis on clinical findings. J. Pediat. **41**: 141, 1952.
54. Dennis, J. L., Hansen, A. E., and Corpening, T. N.: Endocardial fibroelastosis. Pediatrics **12**: 130, 1953.
55. Johnson, F. R.: Anoxia as cause of endocardial fibroelastosis in infancy. A.M.A. Arch. Path. **54**: 237, 1952.

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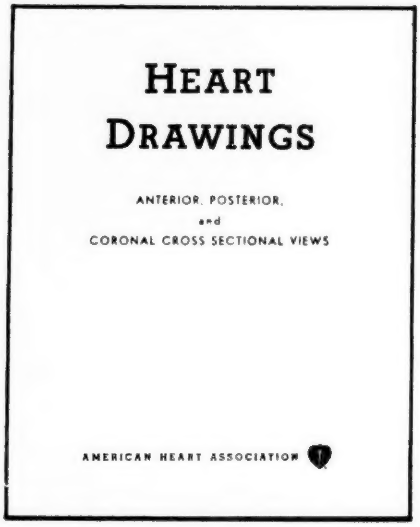

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